

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 August 2000 (02.08.00)	
International application No. PCT/NL99/00783	Applicant's or agent's file reference 9873WO
International filing date (day/month/year) 17 December 1999 (17.12.99)	Priority date (day/month/year) 22 December 1998 (22.12.98)
Applicant QUAEDFLIEG, Peter, Jan, Leonard, Mario et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
23 May 2000 (23.05.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election
- ☒
- was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p>	<p>Authorized officer Juan Cruz</p>
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To: Ms. M.S.N. Jacobs
OCTROOIBUREAU DSM
P.O. Box 9
6160 MA Geleen

DSM P&T		
18 JAN. 2000		
BA	Fig. TB	Serial Nr. 030812

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing (day/month/year)
17 January 2000 (17.01.2000)

Applicant's or agent's file reference
9873WO

IMPORTANT NOTIFICATION

International application No.
PCT/NL99/00783

International filing date (day/month/year)
17 December 1999 (17.12.1999)

Priority date (day/month/year)
22 December 1998 (22.12.1998)

Applicant
DSM N.V. et al.

Title of the invention
Process for the preparation of compounds with enhanced optical purity

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

- ☒ was transmitted to the International Bureau on 21 January 2000 (21.01.2000)
- ☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau *:
- ☐ because the necessary national security clearance has not yet been obtained.
- ☐ because (reason to be specified):

* The international Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/400) if it has not been received. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 20.5(c)).

Name and mailing address of the receiving Office
Bureau voor de Industriële Eigendom
P.O. Box 5820
2280 HV Rijswijk
The Netherlands

Facsimile No. +31703986507

Authorized officer

M. van Bree

Telephone No. +31703986487

PATENT COOPERATION TREATY

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REC'D 18 JAN 2001

WIPO

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 9873WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/NL99/00783	International filing date (day/month/year) 17/12/1999	Priority date (day/month/year) 22/12/1998
International Patent Classification (IPC) or national classification and IPC C12N15/55		
Applicant DSM N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 23/05/2000	Date of completion of this report 16.01.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Döpfer, K-P Telephone No. +49 89 2399 8547



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL99/00783

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1,3-16	as originally filed	
2	with telefax of	18/10/2000

Claims, No.:

1-11	as originally filed
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2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/NL99/00783

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL99/00783

Re Item I

Basis of the report

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: US-A-4 745 067 (UMEZAWA HAMAO ET AL) 17 May 1988 (1988-05-17)
D2: WO 98 50575 A (NG JOHN S ;SEARLE & CO (US); WANG PING T (US);
LANDIS BRIAN H (US)) 12 November 1998 (1998-11-12)
D3: BECKER ET AL: 'Structure of peptide deformylase and identification of the
substrate binding site' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273,
no. 19, 8 May 1998 (1998-05-08), pages 11413-11416, XP002104183 cited
in the application

2. The present application relates to a method for the preparation of chiral compounds with enhanced optical purity by (i) reacting a compound of the general formula $R_1-C^*(R_2)(Y)-NH-CHO$ (I) with an enzyme with peptide deformylase activity and (ii) the formylation of an amino compound of the general formula $R_1-C^*(R_2)(Y)-NH_2$ (II) with an enzyme with peptide deformylase activity.

3. Novelty (Article 33(2) PCT)

D1 discloses L-aminoacylases which act enantioselectively on the L-isomers of N-acylated amino acid derivatives. These L-aminoacylases exhibit also activity towards N-formyl-L-amino acids. The document shows also the influence of divalent metal ions on the enzyme stability and activity. The activity of these L-aminacylases S1 and S2 towards N-formylated substrates is rather low (cf Tables 1 and 4, respectively).

D2 relates to a method for the preparation of chiral β -amino acids by contacting

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL99/00783

said amino acids with an acyl donor and Penicillin G acylase. No activity which could be regarded as peptide deformylase is reported.

D3 addresses the structure of peptide deformylase (EC 3.5.1.27) and identification of the substrate binding site. The sequences HEXHH, EGCLS, GXGXAAXQ are mentioned in the present application (cf claim 5). Nevertheless, the use of this enzyme in a method for the enrichment of an enantiomer has not been disclosed.

None of the prior art documents discloses a method using an enzyme with peptide deformylase activity as defined at page 3 (lines 21-28) of the present application. Thus, the subject-matter of present claims 1-11 is regarded as novel.

4. Inventive step (Article 33(3) PCT)

D1 is considered representing the closest prior art (see Point V.3 of this Report). The problem underlying the present application can be regarded as to provide an alternative method for the production of chiral compounds with improved optical purity. The solution presented by the present application is the use of peptide deformylase enzymes either by formylating or deformylating enantioselectively the corresponding starting compounds of the general formulae (I) and (II). D1 gives the hint for the enantioselectivity of deformylase reactions. But the enzyme used (L-aminoacylase) does not exhibit sufficient activity towards N-formylated amino acids to achieve the desired result, i.e. to obtain an enantiomeric excess useful in the production of compounds with "enhanced" optical purity. D1 does not provide information on the influence of divalent metal ions on the deprotection and enantioselectivity of N-formyl amino acids either. In the first view D3 appears to provide the essential information concerning the structural properties of the enzyme required for the desired activity. But the prior art document is silent with respect to activity and enantioselectivity of the enzyme investigated. The conclusion is therefore, the skilled person dealing with the technical problem posed would not come to the claimed method by combining the teachings of documents D1 and D3. Thus, the subject-matter of present claims 1-11 is regarded as involving an inventive step (Article 33(3) PCT).

4. Industrial applicability (Article 33(4) PCT)

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL99/00783

The subject-matter of present claims 1-11 appear to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

1. The term "...enhanced optical purity..." with its **unlimited** use in claims 1 and 2 (any minimal enantiomeric excess would fall under the scope of the present claims) is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the scope of said claims unclear (Article 6 PCT).

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 9873W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/NL 99/ 00783	International filing date (day/month/year) 17/12/1999	(Earliest) Priority Date (day/month/year) 22/12/1998
Applicant DSM N.V. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**PROCESS FOR THE ENZYMATIC PREPARATION OF AMINO ACID DERIVATIVES WITH
ENHANCED OPTICAL PURITY**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/NL 99/00783

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/55 C12P13/04 C12P41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12P C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 745 067 A (UMEZAWA HAMAO ET AL) 17 May 1988 (1988-05-17) tables 1,2,4	1
A	tables 1,2,4	2
A	WO 98 50575 A (NG JOHN S ; SEARLE & CO (US); WANG PING T (US); LANDIS BRIAN H (US)) 12 November 1998 (1998-11-12) examples 1-3	2
A	BECKER ET AL: "Structure of peptide deformylase and identification of the substrate binding site" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 19, 8 May 1998 (1998-05-08), pages 11413-11416, XP002104183 cited in the application page 11415 -page 11416; figure 1	1,2,4-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

G document member of the same patent family

Date of the actual completion of the international search

4 April 2000

Date of mailing of the international search report

12/04/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

van Klompenburg, W

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/NL 99/00783

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4745067	A	17-05-1988	AT 65796 T	15-08-1991
			DE 3680574 A	05-09-1991
			EP 0201039 A	12-11-1986
			JP 2084435 C	23-08-1996
			JP 7106150 B	15-11-1995
			JP 63022188 A	29-01-1988
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WO 9850575	A	12-11-1998	AU 7359198 A	27-11-1998
			EP 0979303 A	16-02-2000
<hr/>				